REMARKS

Status of the Claims

Claims 1-3, 7, 8, 10-18, and 26-36 are now pending in the application. Claims 4-6, 9, and 19-25 have been cancelled without prejudice or disclaimer because they are drawn to non-elected inventions. Claims 1, 2, 7, 10, 11, 12, 14, and 16 have been amended. Support for the amendments to these claims may be found in the specification in the last paragraph of page 15, the first full paragraph of page of page 17, and the first full paragraph of page 30. Support for new claims 26-36 may be found in original claims 1 and 7. No new matter has been added by amendment. Reexamination and reconsideration of the claims are respectfully requested.

The Restriction Requirement

Applicants affirm the election with traverse of the claims of Group I as directed to SEQ ID NO:1 and nucleotide sequences encoding SEQ ID NO:2. Applicants expressly reserve the right to file divisional applications or take such other appropriate measures deemed necessary to protect the inventions in the remaining claims and species.

The Objections to the Claims Should be Withdrawn

Claims 7 and 8 were objected to for depending from non-elected claim 5. Claim 7 has been amended so that it no longer depends from a non-elected claim, thereby obviating the objection.

The Rejections Under 35 U.S.C. 112, First Paragraph Should be Withdrawn

The Examiner has rejected claims 1-3 and 16-18 under 35 U.S.C. § 112, first paragraph, on the grounds that they contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is traversed as applied to these claims and to the extent that it applies to new claims 26-29 and 32-35 for the reasons described below.

The Examiner states, "The specification . . . sets forth a proposed region corresponding to the *Bt* toxin binding site for the genus, yet there is no correlation or nexus provided between possession of this structural feature and the encompassed functional features of SEQ ID NO:1 such that it is clearly conveyed that possession of any polypeptide having this structural region in common would possess *Bt* toxin receptor biological activity." (February 13, 2002 Office Action, page 3). Accordingly, the premise of the Examiner's argument is that Applicants must demonstrate that every sequence falling within the structural limitations set forth in the claims will possess the functional limitation set forth in the claims in order to adequately describe the claimed genus. However, the requirement set forth in the office action is not supported by the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, ¶ 1, 'Written Description' Requirement" (66 Fed. Reg. 1099 (2001)) or the supporting case law.

The "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, 'Written Description' Requirement" state that genus may be described by "sufficient description of a representative number of species . . . or by disclosure of relevant, identifying characteristics , *i.e.* structure or other physical and/or chemical properties." *Id.* at 1106. Furthermore, the Guidelines state that "[d]isclosure of any combination of . . . identifying characteristics that distinguish the claimed invention from other materials and would lead one to the conclusion that the applicant was in possession" of the claimed invention is sufficient to satisfy the written description requirement. *Id.* at 1106.

Applicants submit that the written description provided for the sequences recited in claims 1-3, 16-18, 26-29 and 32-35 meets this requirement. The claims recite the identifying structural characteristics that define each genus of nucleotide sequences or amino acid sequences. Claims 1-3, 16-18, and 26-29, and 32 recite nucleotide sequences having at least 60%, 70%, 75%, 85%, or 95% sequence identity with the nucleotide sequence set forth in SEQ ID NO:1, nucleotide sequences that hybridize to the nucleotide sequence set forth in SEQ ID NO:1 under stringent conditions, and nucleotide sequences consisting of at least 22 contiguous nucleotides of the nucleotide sequence set forth in SEQ ID NO:1. Claims 33-35 recite nucleotide sequences encoding a fusion polypeptide comprising at least one polypeptide of interest and a polypeptide having at least about 75%, at least about 85%, or at least about 95% sequence identity with the

amino acid sequence set forth in SEQ ID NO:2. These structural limitations are sufficient to distinguish the claimed nucleotide sequences from other materials and thus sufficiently define the claimed genus.

Furthermore, in *Regents of the University of California v. Eli Lilly & Co*, 119 F.3d 1559 (Fed. Cir. 1997), the court held that "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." 119 F.3d at 1569. The recitation of the structural features of sequence identity with SEQ ID NO:1 or SEQ ID NO:2, hybridization with SEQ ID NO:1, or the presence of subsequences of SEQ ID NO:1 of a given minimum length is sufficient to satisfy this requirement.

Applicants have further provided the functional characteristics that distinguish the claimed sequences of the genus. Specifically, the claims recite that the variants and fragments of SEQ ID NO:2 have *Bt* toxin binding activity. Accordingly, both the structural properties and the functional properties that characterize the claimed genus are specifically recited in the claims.

The present claims are analogous to those presented in Example 14 of the Revised Interim Written Description Guidelines. Example 14 is directed to a generic claim: a protein having at least 95% sequence identity to the sequence of SEQ ID NO:3, wherein the sequence catalyzes the reaction A → B. The conclusion in the Training Materials is that the generic claim of Example 14 is sufficiently described under § 112, first paragraph, because 1) "the single sequence disclosed in SEQ ID NO:3 is representative of the genus" and 2) the claim recites a limitation requiring the compound to catalyze the reaction from A → B. The conclusion in the Guidelines is that one of skill in art would recognize that the Applicants were in possession of the necessary common attributes possessed by the members of the genus.

Following the analysis of Example 14, Applicants submit that claims 1-3, 16-18, 26-29 and 32-35 satisfy the written description requirements of § 112, first paragraph. Specifically, the claims of the present invention encompass nucleotide sequences having sequence identity to the nucleotide sequence of SEQ ID NO:1, hybridizing under stringent conditions to the nucleotide sequence of SEQ ID NO:1, comprising a subsequence of SEQ ID NO:1, or encoding a

polypeptide having sequence identity with SEQ ID NO:2, wherein the claimed sequences encode a polypeptide having a specified activity. As in Example 14, the specification discloses the nucleic acid sequence of SEQ ID NO:1, and the claims recite a limitation requiring the compound to have a specific function (*i.e.*, *Bt* toxin binding activity). Accordingly, claims 1-3, 16-18, 26-29, and 32-35 provide the relevant, identifying characteristics that describe the claimed genus, and one of skill in the art would recognize that the inventors were in possession of the claimed invention.

Claims 1-3 and 16-18 were rejected under 35 U.S.C., § 112, first paragraph, on the grounds that the specification does not provide sufficient enablement to allow one of skill in the art to make and use the claimed invention. The rejection is traversed as applied to these claims and to new claims 26-29 and 32-35 for the reasons described below.

The Examiner argues that the specification does not enable one of skill in the art to make nucleotide sequences encoding fragments or variants of the polypeptide shown in SEQ ID NO:2 because Applicants do not teach which amino acids of SEQ ID NO: 2 may be altered while still retaining the *Bt* toxin receptor activity of this polypeptide. In fact, sufficient guidance for making and using the recited variants and fragments is given in the specification. Applicants have provided a sequence of the wild type ECB *Bt* toxin receptor in SEQ ID NO:2. The variant and fragment nucleotide sequences of claims 1-3, 16-18, 26-29, and 32-35 vary from the nucleotide sequence set forth in SEQ ID NO:1 by structural parameters (i.e. the claimed nucleotide sequences share a specified percent sequence identity to SEQ ID NO:1, hybridize to SEQ ID NO:1 under stringent conditions, or consist of at least 22 contiguous nucleotide sequences of SEQ ID NO:2) that are defined in the specification, and the claims recite that the claimed variants and fragments encode polypeptides having the functional properties (i.e. the *Bt* toxin binding properties) of the polypeptide having the amino acid sequence set forth in SEQ ID NO:2. Guidance for determining percent sequence identity and hybridization under stringent conditions is provided in the specification (see, pages 23-31.). The specification also describes conservatively-modified variants of the disclosed polypeptide and conservative substitutions of amino acids. S*ee*, the top of page 18.

In addition to the ECB *Bt* toxin receptor polypeptide of SEQ ID NO:2, the specification discloses two additional working examples of insect *Bt* toxin receptor polypeptides in SEQ ID NOS: 4 and 6. A comparison of these three *Bt* toxin receptor polypeptides can be used to identify conserved regions that are likely to be required for receptor function. The specification describes functional motifs found in the disclosed *Bt* toxin receptors on page 35. The specification also provides methods for using mutagenesis and sequence shuffling to identify functional *Bt* receptor variants. *See*, last paragraph on page 17 and first full paragraph of page 19.

Finally, the specification provides assays for *Bt* toxin binding and toxicity assays. *See*, last paragraph of page 5 and Example 3 on pages 36-37. Thus, a rational scheme for determining the regions of the ECB *Bt* toxin receptor that would tolerate modification is provided. Based on the regions of SEQ ID NO:2 that are conserved with other *Bt* toxin receptor family members and the guidance provided in the specification regarding *Bt* toxin receptor functional domains, the skilled artisan could choose among possible modifications to produce polypeptides within the structural parameters set forth in the claims and then test these modified variants to determine if they retain the *Bt* toxin binding activity of the polypeptide given in SEQ ID NO:2. Although some quantity of experimentation would be required, the level of experimentation would not be undue in view of the amount of direction provided in the specification, the presence of working examples, the state of the prior art for *Bt* toxin receptor sequences, and the level of skill of one of ordinary skill in the art. Further, the claims are directed only to those variants and fragments that retain the *Bt* toxin binding activity of the polypeptide having the amino acid sequence set forth in SEQ ID NO:2. These factors all favor a conclusion that one of skill in the art could practice the claimed invention without undue experimentation and that the specification provides enablement commensurate with the scope of the claims.

In rejecting the instant claims for lack of enablement, the Examiner cites Skolnick and Fetrow (2000) *Trends in Biotechnology* 18:34-39 in support of the argument that the function of a protein cannot be predicted based on its tertiary structure. However, the function of the *Bt* toxin receptor has not been determined based on the presence of any particular three-dimensional

structural feature. Rather, the function of this receptor has been determined based on sequence similarity with known *Bt* toxin receptor polypeptides, and on the presence of a consensus domain for toxin binding. *See*, Example 1 on pages 33-35 of the specification. Accordingly, the criticisms regarding the accuracy of methods of predicting protein function based on three-dimensional structure provided by Skolnick and Fetrow are not applicable to the methods of function prediction used by the Applicants of the present application.

Furthermore, while applicants agree that some regions of a protein must retain a certain conformation in order for the protein to be active, it does not follow that a protein's tertiary structure must be known in order to determine the activity of that protein. In fact, three-dimensional structures have been elucidated for only a very few of the thousands of proteins having known biochemical or physiologic activity. Accordingly, the teachings regarding structural predictions found in Skolnik and Fetrow are not relevant to methods for predicting protein function used by the Applicants.

In view of the above arguments and amendments, all grounds for rejection under 35 U.S.C. § 112, first paragraph have been obviated or overcome. Reconsideration and withdrawal of the rejections are respectfully requested.

The Rejections Under 35 U.S.C. § 112, Second Paragraph, Should be Withdrawn

Claims 7-8, 10-11, 14, and 16 were rejected under 35 U.S.C. § 112, second paragraph, on the grounds that they are indefinite for reciting a "a cell of interest." Applicants submit that one of skill in the art would understand the metes and bounds of this phrase. Nevertheless, to expedite prosecution, claims 7 and 10 have been amended to recite that the claimed expression cassettes comprise a promoter capable of initiating transcription of the nucleotide sequence. Support for this amendment may be found in the last paragraph of page 9. Similarly, claims 14 and 16 have been amended such that they recite a "cell."

Claims 2 and 3 were rejected under 35 U.S.C. § 112, second paragraph, on the grounds that they are indefinite because they refer to a toxin without proper antecedent basis. The

Applicants acknowledge the error noted by the Examiner, and have amended claim 1, from which claims 2 and 3 depend, to provide proper antecedent basis for this term.

In view of the above arguments and amendments, all grounds for rejection under 35 U.S.C. § 112, second paragraph have been overcome. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

Consideration Of Previously Submitted Information Disclosure Statement

It is noted that initialed copies of the PTO Forms 1449 that were submitted with Applicants' Information Disclosure Statements filed April 20, 2001 and September 21, 2001 have not been returned to Applicants' representative with the Office Action. Accordingly, it is requested that an initialed copy of each of the Form 1449s be forwarded to the undersigned with the next communication from the PTO. In order to facilitate review of the references by the Examiner, a copy of each of the Information Disclosure Statements and the Form 1449s are attached hereto. Copies of the cited references were provided at the time of filling the original Information Disclosure Statement, and, therefore, no additional copies of the references are submitted herewith. Applicants will be pleased to provide additional copies of the references upon the Examiner's request if it proves difficult to locate the original references.

CONCLUSION

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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1. (Amended) An isolated nucleic acid molecule having a nucleotide sequence encoding a polypeptide having *Bt* toxin binding activity [receptor], wherein said nucleotide sequence is selected from the group consisting of:

a) [a] the nucleotide sequence set forth in SEQ ID NO: 1[, SEQ ID NO: 3 or SEQ ID NO: 5];

b) a nucleotide sequence having at least about 60 % identity to the nucleotide sequence of a);

c) a nucleotide sequence having at least about 70 % identity to the nucleotide sequence of a);

d) a nucleotide sequence having at least about 75 % identity to the nucleotide sequence of a);

e) a nucleotide sequence having at least about 85 % identity to the nucleotide sequence of a);

f) a nucleotide sequence having at least about 95 % identity to the nucleotide sequence of a);

g) a nucleotide sequence consisting of at least 22 contiguous nucleotides of the nucleotide sequence set forth in SEQ ID NO:1;

[h) a nucleotide sequence consisting of at least about 15 contiguous nucleotides of the nucleotide sequence set forth in SEQ ID NO:3, or SEQ ID NO:5 ;

i)]h) a nucleotide sequence that hybridizes under stringent conditions to the nucleotide sequence of a), said stringent conditions comprising hybridization in 50% formamide, 1 M NaCl, 1% SDS at 37°C, followed by a wash in 0.1X SSC at 60 to 65°C; and

i) a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO:2.

2. (Amended) The nucleic acid molecule of claim 1, wherein said *Bt* toxin is a Cry1A toxin.

7. (Amended) An expression cassette comprising a nucleotide sequence encoding a

[the]fusion polypeptide comprising at least one polypeptide of interest and a polypeptide selected from the group consisting of: [of claim 5,]

a) a polypeptide having the amino acid sequence set forth in SEQ ID NO:2;

b) a polypeptide having at least about 52% sequence identity to the amino acid sequence set forth in SEQ ID NO: 2, wherein said polypeptide has *Bt* toxin binding activity;

c) a polypeptide having at least about 60% sequence identity to the amino acid sequence set forth in SEQ ID NO:2, wherein said polypeptide has *Bt* toxin binding activity;

d) a polypeptide having at least about 70% sequence identity to the amino acid sequence set forth in SEQ ID NO:2, wherein said polypeptide has *Bt* toxin binding activity;

e) a polypeptide having at least about 75% sequence identity to the amino acid sequence set forth in SEQ ID NO:2, wherein said polypeptide has *Bt* toxin binding activity;

f) a polypeptide having at least about 85% sequence identity to the amino acid sequence set forth in SEQ ID NO:2, wherein said polypeptide has *Bt* toxin binding activity;

g) a polypeptide having at least about 95 % sequence identity to the amino acid sequence set forth in SEQ ID NO:2, wherein said polypeptide has *Bt* toxin binding activity;

h) a polypeptide consisting of at least about 15 contiguous residues of the amino acid sequence set forth in SEQ ID NO:2, wherein said polypeptide has *Bt* toxin binding activity; and

i) a polypeptide encoding a nucleotide sequence according to claim 1;

wherein said nucleotide sequence encoding the fusion polypeptide is operably linked to a promoter capable of initiating the transcription of the nucleotide sequence[that drives expression in a cell of interest].

10. (Amended) An expression cassette comprising at least one nucleotide sequence according to claim 1, wherein said nucleotide sequence is operably linked to a promoter capable of initiating the transcription of the nucleotide sequence [that drives expression in a cell of interest].

11. (Amended) The expression cassette of claim 10, wherein said promoter is capable

of initiating the transcription of the nucleotide sequence in [cell of interest is]an insect cell or a mammalian cell.

12. (Amended) The expression cassette of claim 10 wherein said promoter is capable of initiating the transcription of the nucleotide sequence in[cell of interest is] a microorganism.

14. (Amended) A vector for delivery of a nucleotide sequence to a cell [of interest], the vector comprising at least one nucleotide sequence according to claim 1.

16. (Amended) A transformed cell [of interest] having stably incorporated within its genome a nucleotide sequence according to claim 1.[selected from the group consisting of:

a) a nucleotide sequence set forth in SEQ ID NO: 1, SEQ ID NO: 3 or SEQ ID NO: 5;

b) a nucleotide sequence having at least about 60 % identity to the nucleotide sequence of a);

c) a nucleotide sequence having at least about 70 % identity to the nucleotide sequence of a);

d) a nucleotide sequence having at least about 75 % identity to the nucleotide sequence of a);

e) a nucleotide sequence having at least about 85 % identity to the nucleotide sequence of a);

f) a nucleotide sequence having at least about 95 % identity to the nucleotide sequence of a);

g) a nucleotide sequence consisting of at least 22 contiguous nucleotides of the nucleotide sequence set forth in SEQ ID NO:1;

h) a nucleotide sequence consisting of at least about 15 contiguous nucleotides of the nucleotide sequence set forth in SEQ ID NO:3, or SEQ ID NO:5 ;

i) a nucleotide sequence that hybridizes under stringent conditions to the nucleotide sequence of a); and]